

# ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

Section Editor: William D. Chey, MD

## Diet and Irritable Bowel Syndrome



William D. Chey, MD  
 Timothy T. Nostrant Professor of Gastroenterology & Nutrition  
 Division of Gastroenterology  
 Director, GI Physiology Laboratory  
 Director, Digestive Disorders Nutrition & Behavioral Medicine Program  
 University of Michigan Health System  
 Ann Arbor, Michigan

### G&H What is food intolerance?

**WC** Food intolerance refers to a condition in which patients develop an adverse outcome as a consequence of eating certain foods. It is important to recognize that food intolerances can be either gastrointestinal- or nongastrointestinal-related. For example, many patients describe symptoms akin to irritable bowel syndrome (IBS), such as abdominal pain or discomfort, bloating, or altered bowel habits, after eating. Notably, food intolerances can be associated with constipation as well as diarrhea. Other patients may develop a myriad of nongastrointestinal-related symptoms, such as brain fog, depression, joint pain, or skin rash.

### G&H What are the proposed pathways between food intolerance and symptoms of IBS?

**WC** There are multiple pathways that might link food intolerance to IBS symptoms—osmotic and fermentation effects, alterations in neurohormonal or gut immune function, changes in the gut microbiome, or permeability, for example. It is important to keep in mind that food is an amalgam of many different constituent components, many of which can affect gut function and sensation. Food is complicated; wheat provides a great example. A common misconception is that wheat intolerance is the consequence of gluten sensitivity. However, a

double-blind, placebo-controlled study that was recently published in *Gastroenterology* demonstrated that more patients who report a sensitivity to wheat are actually experiencing reactions to fructan, the main carbohydrate in wheat, than to the protein gluten. The nocebo response also plays a role in some patients with food intolerance. In other words, if an individual believes that certain foods will worsen his or her symptoms, there is a greater likelihood that food will indeed worsen those symptoms. Further, there are likely other antigens in food beyond gluten that, in a susceptible individual, might trigger an immunologic response and cause gastrointestinal symptoms. A number of commercially available tests (eg, antigen leukocyte cellular antibody test, Cell Sciences System; mediator release testing, Oxford Biomedical Technologies; immunoglobulin G [IgG] antibody testing) rely upon gut immune activation to different types of food. A randomized, controlled trial of 58 patients found that an exclusion diet based on leukocyte activation led to better outcomes compared to a matched comparison diet. The results were compelling, but were from a single study with a small sample size. Almost no data are available for mediator release testing, and only outdated data exist for IgG antibody testing. A large-scale, multicenter study assessing IgG antibody testing as a means of choosing an exclusion diet is starting soon and should provide credible data within the next year, but more data are needed overall to support the use of these tests.

## G&H What are the most common dietary approaches for the management of IBS?

**WC** There are many IBS patients for whom food is an important trigger. Of the various food-related triggers, carbohydrates are most commonly identified by patients as problematic. Chief among culprit carbohydrates are the fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs), which are difficult, if not impossible, for the human small intestine to digest or absorb. Upon reaching the colon, FODMAPs are fermented by bacteria to produce gases and short-chain fatty acids, triggering symptoms in patients with IBS who have underlying abnormalities and motility and visceral sensation. The low-FODMAP diet is a popular approach to improve symptoms in patients with IBS.

My colleagues and I conducted a survey of approximately 1500 US gastroenterologists from the American College of Gastroenterology (ACG) mailing list; the results are currently in press in the *Journal of Neurogastroenterology and Motility*. We found that the majority of US gastroenterologists are employing some form of dietary therapy in their IBS patients. Of the therapies that they are using, the most popular is a low-FODMAP diet. Interestingly, while clinicians tended to recommend a low-FODMAP diet more often than a gluten-free diet, patients were utilizing a gluten-free diet more commonly than a low-FODMAP diet. Although there are some data to suggest that a subset of IBS patients improve with a gluten-free diet, the data supporting a gluten-free diet are not nearly as robust as the data supporting a low-FODMAP diet.

## G&H Are there any other dietary approaches that can be taken to treat or manage symptoms of IBS?

**WC** Many patients experiment with diets based upon carbohydrate exclusion, such as the Specific Carbohydrate Diet. The Paleo Diet is also popular, as is the South Beach or other low-carbohydrate diets. Unfortunately, most of these dietary approaches are not evidence-based.

## G&H What are the benefits and limitations of the low-FODMAP approach?

**WC** Multiple randomized, controlled trials have shown that the low-FODMAP diet is beneficial for the overall and individual symptoms of IBS. In particular, pain and bloating seem to be the most responsive symptoms. My colleagues and I published a study last year reporting a 2-fold increase in the likelihood of a clinically meaningful improvement in disease-specific quality of life, as

measured by the Irritable Bowel Syndrome Quality of Life Instrument, in patients on the low-FODMAP diet compared to usual dietary recommendations. All of these studies have focused solely on the efficacy of excluding FODMAPs from the diet vs a comparator, such as placebo, another diet, or a high-FODMAP diet. However, the low-FODMAP diet is a 3-phase plan; the other 2 phases of the plan, determining sensitivities and personalization, have not been studied in clinical trials.

Preliminary data suggest that the low-FODMAP diet exerts a variety of effects on the colonic microbiome. Studies examining the stool microbiome have found 2 fairly consistent effects: a reduction in *Bifidobacterium* species, which are thought to be potentially beneficial bacteria in the colon, and a reduction in the levels of fecal butyrate, which is considered an important nutrient not only for the bacteria in the colon but also for the colonic epithelium. The impact of these changes—bad, good, or indifferent—is unknown; what is certain is that the microbiome is altered. There is some cause for concern in regard to the changes that have been observed, and, thus, clinicians should do everything possible to try to minimize the impact of the diet on the colonic microbiome.

## G&H Can you further explain the 3 phases to the low-FODMAP diet?

**WC** There are 3 phases to the low-FODMAP diet, and exclusion is the beginning, not the end. The acronym that I have coined is ESP: Eliminate, determine Sensitivities, Personalize. If a patient responds to the elimination phase of the diet—which should only last 2 to 6 weeks—then he or she should undergo a structured reintroduction of foods containing individual FODMAPs to determine his or her specific sensitivities. That information should then be leveraged to create a less restrictive, personalized low-FODMAP diet for that patient that can be carried forward. Anything that clinicians can do to make the low-FODMAP diet less restrictive will be much less burdensome for the patient, may increase the likelihood of long-term adherence, and reduce the impact of the diet on the colonic microbiome. The time and effort it takes to administer the low-FODMAP diet properly makes clear the benefits of collaborating with a properly trained registered dietitian.

## G&H Do dietary treatment approaches differ between the various subtypes of IBS?

**WC** Right now, the answer is uncertain. The vast majority of the studies on the low-FODMAP diet have focused on patients with either diarrhea-predominant or

mixed IBS, and there are virtually no data regarding the efficacy of the low-FODMAP diet solely in patients with constipation-predominant IBS. Several small studies include patients with constipation; unfortunately, the sample size, even when all of the studies are combined, is so small that it is difficult to draw any conclusions regarding the efficacy of the diet in that subgroup of IBS. However, my colleagues and I received a grant from the ACG to perform the first randomized, controlled trial dedicated to assessing the efficacy of the low-FODMAP diet in patients with constipation-predominant IBS, which will begin this summer and hopefully be completed within the next 12 to 18 months.

### **G&H** Is there a way to identify which patients might benefit from certain dietary approaches?

**WC** A very simple screen is to ask patients whether their symptoms are related to eating or not. A clinician can gain insight by asking what the typical culprit foods are; many times, patients will say wheat and dairy. Wheat contains fructans and milk contains lactose, both of which are important FODMAPs. Occasionally, patients will say garlic and onions, and, again, those are important clues that the symptoms are FODMAP-related. However, it is not always well understood that garlic and onions are an important source for FODMAPs and a trigger for IBS symptoms for many individuals. Patients who understand that their symptoms are related to food are more likely to respond to dietary therapies than patients who say that their symptoms have nothing to do with eating a meal. The symptoms that are most likely to improve on the low-FODMAP diet are pain and bloating—diarrhea can respond, but benefits are less consistent than for pain and bloating.

Multiple studies now suggest that changes in the microbiome, identifiable before initiating dietary therapy, can determine which patients are more or less likely to respond to the low-FODMAP diet. Thus, in the near future, clinicians may be able to collect a stool sample, assess the microbiome, and then determine the likelihood that a person will or will not respond to the low-FODMAP diet. There are also several interesting studies looking at the metabolic consequences of the interaction between the microbiome and food that suggest that there may be metabolomic signatures that can identify patients who are more likely to respond. One example is the measurement of volatile organic compounds in gases emanated from stool. A study led by Dr Megan Rossi at King's College London suggested that patterns in volatile organic compounds could identify patients who are more likely to improve with the low-FODMAP diet or a probiotic supplement.

### **G&H** Do any guidelines address dietary interventions, or are they likely to?

**WC** The Rome Foundation has addressed dietary interventions for patients with IBS. In fact, I chaired a committee that focused on the role of food in functional gastrointestinal disorders. In 2013, the committee published a series of articles in the *American Journal of Gastroenterology* that discussed the impact of fiber, carbohydrates, proteins, and lipids in the gastrointestinal tract. The most recent set of guidelines from the Rome IV criteria, published in 2016, includes an article by lead author Dr Giovanni Barbara on the role of the intestinal microenvironment, which concerns not just diet but also the microbiome, bile acids, and a variety of factors that reside within the bowel lumen that influence the pathogenesis and illness experience of patients with IBS. Additionally, the ACG will be publishing an evidence-based treatment monograph within the next few months, which will include a systematic review and meta-analysis of diet therapies for IBS, with recommendations that assess the quality of the evidence and the strength of the recommendation.

### **G&H** Have any studies evaluated the efficacy of dietary intervention in pediatric patients?

**WC** A randomized, controlled trial led by Dr Bruno P. Chumpitazi assessed the efficacy of the low-FODMAP diet vs a typical US diet in children with IBS. The authors found clear benefits with the low-FODMAP diet for IBS symptoms. This study is important not only because it is one of the only randomized, controlled trials in pediatric patients, but because it is the first study to demonstrate an association between differences in the microbiome and the likelihood of response with a low-FODMAP diet. As such, it has led to further discussion of leveraging the microbiome as a biomarker to predict response with a low-FODMAP diet.

### **G&H** What are the priorities of research in this field?

**WC** As I mentioned earlier, all of the current literature addresses the elimination phase of the low-FODMAP diet. There is almost no information on how to best administer a structured reintroduction of foods containing FODMAPs or on the longevity of the benefits and safety of the diet with extended use. Another area that deserves research is the incremental cost that is associated with the low-FODMAP diet. It is a topic that has not been well quantified, but we know the diet does cost more. Further work on biomarkers that predict

response to dietary therapies is of considerable interest. Of course, additional trials to understand the efficacy of other elimination diets will be important. Finally, future research should not only focus on elimination but should also consider the possibility of supplementation as a means of improving symptoms in IBS patients. So-called functional foods are in their infancy but hold tremendous potential to expand nutrition-based solutions for patients with IBS.

*Dr Chey serves as a consultant for, and received a research grant from, Nestle Health Science, and has stock options with TrueSelf Foods.*

### Suggested Reading

Ali A, Weiss TR, McKee D, et al. Efficacy of individualised diets in patients with irritable bowel syndrome: a randomised controlled trial. *BMJ Open Gastroenterol.* 2017;4(1):e000164.

Barbara G, Feinle-Bisset C, Ghoshal UC, et al. The intestinal microenvironment and functional gastrointestinal disorders [published online February 18, 2016]. *Gastroenterology.* doi:10.1053/j.gastro.2016.02.028.

Chey WD. The role of food in the functional gastrointestinal disorders: introduction to a manuscript series. *Am J Gastroenterol.* 2013;108(5):694-697.

Chumpitazi BP, Cope JL, Hollister EB, et al. Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome. *Aliment Pharmacol Ther.* 2015;42(4):418-427.

Eswaran S, Chey WD, Jackson K, Pillai S, Chey SW, Han-Markey T. A diet low in fermentable oligo-, di-, and monosaccharides and polyols improves quality of life and reduces activity impairment in patients with irritable bowel syndrome and diarrhea. *Clin Gastroenterol Hepatol.* 2017;15(12):1890-1899.e3.

Lenhart A, Ferch C, Shaw M, Chey WD. Use of dietary management in irritable bowel syndrome: results of a survey of over 1500 U.S. gastroenterologists. *J Neurogastroenterol Motil.* In press.

Rossi M, Aggio R, Staudacher HM, et al. Volatile organic compounds in feces associate with response to dietary intervention in patients with IBS. *Clin Gastroenterol Hepatol.* 2018;16(3):385-391.e1.

Skodje GI, Sarna VK, Minelle IH, et al. Fructan, rather than gluten, induces symptoms in patients with self-reported non-celiac gluten sensitivity. *Gastroenterology.* 2018;154(3):529-539.e2.